REMARKS

Claims 1-54 are pending in the subject application. Applicants note that the Examiner has withdrawn claims 8, 13-24 and 29-47 from further consideration. Applicants have hereinabove cancelled claims 8, 13-24 and 29-47 without prejudice or disclaimer to their right to pursue the subject matter of these claims in a later-filed application. In addition, applicants have amended claims 1-7, 9-12, 25-28 and 48-54. Support for the amendments to claims 1 and 53 may be found inter alia in the specification at page 13, lines 28-32. The remaining changes to the claims merely correct dependency and introduce minor grammatical and format changes. Applicants have further amended the specification to add Sequence identifiers, i.e. SEQ ID NOs. In making these amendments, applicants neither concede the correctness of the Examiner's objections and rejections, nor abandon their right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application. Applicants maintain that these amendments raise no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 1-7, 9-12, 25-28 and 48-54 will be pending and under examination.

In view of the amendments and arguments set forth below, applicants maintain that the Examiner's objections and rejections have been overcome and respectfully request that the Examiner reconsider and withdraw same.

Objection to the Specification

The Examiner stated that the nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. §§ 1.821 - 1.825. The Examiner stated that page 29 of the specification comprises sequences of primers. The Examiner stated that SEQ ID NOs. must be assigned to these sequences. The Examiner stated that it is noted that sequences provided in computer readable format (CRF) and on paper and a statement indicating that the sequences on CRF and paper are the same were filed by applicant on July 19, 2004. The Examiner stated that however, there is no indication to what these filed sequences correspond to. The Examiner stated that if the paper sequence listing and CRF include the sequences on page 29, amendment of the specification to include the appropriate SEQ ID NOs will place this application in compliance with 37 C.F.R. §§ 1.821-1.825. The Examiner stated that if these sequences are not part of the sequence listing, new sequence listings must be filed.

In response, applicants respectfully traverse. Applicants note that the sequences on page 29 of the subject specification are the sequences set forth in the Sequence Listing filed on July 19, 2004 in connection with the subject application. Therefore, no new Sequence Listing is required. Applicants have hereinabove amended the specification to include references to the sequence identifier information (i.e., SEQ ID NO:) as required by 37 C.F.R. §1.821(d). This amendment does not involve any issue of new matter. Therefore, entry of this amendment is respectfully

requested.

In view of the above remarks, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection.

Claim Objections

The Examiner objected to claims 4-7, 9-12, 25-28, 48, 51 and 52 are under 37 C.F.R. §1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. The Examiner stated that accordingly, claims 4-7, 9-12, 25-28, 48, 51 and 52 have not been further treated on the merits.

During a November 20, 2006 telephone conference between Maria Marucci, Esq. of the undersigned attorney's office and Examiner Hama, the Examiner stated that she would consider claims 4-7, 9-12, 25-28, 48, 51 and 52 on the merits once the claim dependencies were corrected. Applicants wish to thank the Examiner for her time.

Applicants note that claims 4-7, 9-12, 25-28, 48, 51 and 52 have been amended to address the Examiner's objection. Therefore, the Examiner's objection is now moot. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of objection and examine amended claims 4-7, 9-12, 25-28, 48, 51 and 52 on the merits.

Claim Rejections Under 35 U.S.C. §101

The Examiner rejected claims 1-3, 49, 50, 53 and 54 under 35 U.S.C. §101 because the claimed invention is allegedly directed to non-statutory subject matter. The Examiner stated that the claims are drawn to adult multipotent human stem cells. The Examiner stated that the claims, as they read, encompass cells which have not seen "the hand of man". The Examiner stated that using the words "isolated" or "cultured" to describe the cells would be remedial.

In response to the Examiner's rejection, applicants respectfully traverse. Claims 1, 49, 50 and 53, as amended, provide "isolated" adult multipotent human stem cells. The claimed "isolated" adult multipotent human stem cells do not occur in nature. Thus, applicants maintain that claims 1, 49, 50 and 53, as amended, and claims 2, 3 and 54 which depend therefrom, are directed to statutory subject matter.

In view of the above remarks, applicants maintain that claims 1-3, 49, 50, 53 and 54 satisfy the requirements of 35 U.S.C. §101. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 1-3, 53 and 54 are under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to

particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner stated that claims 1 and 53 use the term, "significant telomerase activity." The Examiner stated that it is unclear what metes and bounds are envisioned by "significant." The Examiner stated that claims 2, 3, 54 depend on claims 1 and 53 and thus have been included in the rejection.

In response, applicants respectfully traverse. Nevertheless, applicants without conceding the Examiner's position and to expedite prosecution of the subject application, have hereinabove amended claims 1 and 53 by adding the terms "*of at least 20% to 50% of the telomerase activity of the HEK293T transformed cell line*" to further describe the "significant telomerase activity." Therefore, applicants contend that claims 1and 53, and claims 2, 3 and 54 which depend therefrom, satisfies the requirements of 35 U.S.C. §112, second paragraph. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejections Under 35 U.S.C. §102(b)

Katz et al. (PCT Publication No. WO 00/53795)

The Examiner rejected claims 1-3, 49, 50, 53 and 54 under 35 U.S.C. §102(b) as allegedly anticipated by Katz et al. (PCT Publication No. WO 00/53795, published September 14, 2000).

The Examiner alleged that WO 00/53795 discloses human lipo-derived stem cells (Example 1 of WO 00/53795) which can

differentiate into adipocytes, osteocytes, myocytes or chondrocytes, and that the telomerase activity was similar to that exhibited by previously reported human stem cells.

The Examiner acknowledges that WO 00/53795 does not specifically teach that the cells have an HLA class I negative phenotype, a normal karyotype, a capacity to become quiescent and a capacity for self-renewal preserved for at least 130 population doublings. However, the Examiner considers that these characteristics would be inherent to the cell isolated by Katz et al.

Similarly, with regard to claims 53 and 54, the Examiner acknowledges that WO 00/53795 does not specifically teach that the cells, following quiescence, have a phenotype which is class I negative, Class II negative, CD3 negative and CD13 positive, LIF-R negative, Oct-4 positive, Rex-1 positive ad ABCG2 positive, but again considers that these characteristics would be inherent to the cell isolated by WO 00/53795.

In response, applicants respectfully traverse. Applicants respectfully submit that WO 00/53795 does not anticipate the present claims. The cells described in WO 00/53795 do not possess all the elements recited in the pending claims.

Adipose-derived multipotent cells do not all necessarily and inherently possess the claimed characteristics, as can be seen for example in Katz et al. (*Stem Cells* 23: 412-423 (2005)) (hereinafter "Katz II") which is attached hereto as **Exhibit A**.

In particular, it is noted that "Katz II" describes the isolation of multipotent populations of cells from adipose tissue using a method similar to that recited in WO 00/53795. The cells thereby obtained are characterized for cell surface and transcriptional markers and are found to be *inter alia*: **MHC Class I positive** (see "Katz II", page 416, right hand column: "HLA-ABC" and Table 4). Moreover, the cells are **telomerase negative** and **ABCG2 negative** (see "Katz II", page 422, left hand column and Abstract).

It can thus be concluded that not all multipotent cell populations derived from adipose tissue have the claimed characteristics, which include, for pending claim 1, an MHC Class I negative and telomerase positive phenotype, and for pending claim 53, an MHC Class I negative, telomerase positive and ABCG2 positive phenotype. Consequently, these elements, which are recited in applicants' claims, are *not* inherent characteristics of adipose "stem" cells.

The following is also noted with reference to the disclosure of WO 00/53795 compared to the elements recited in present claim 1:

Significant telomerase activity: While WO 00/53795 indicates at page 18 (Example 1) that the cells showed telomerase activity, the measurement of this activity was made before carrying out successive passages, and was detected in the heterogeneous cell population. No measurement was made after successive passages. Consequently, there is no information

with regard to the conservation of telomerase activity throughout at least 130 population doublings, as required by pending claim 1. Furthermore, telomerase activity was not measured in a homogeneous or clonal population. Therefore, the activity cannot be unambiguously attributed to a single multipotent cell. Consequently, WO 00/53795 does not describe cells having the required telomerase activity.

HLA Class I negative phenotype: WO 00/53795 contains no explicit information as to whether the cells have an HLA Class I negative phenotype. As pointed out above, this characteristic is *not* an inherent feature of multipotent adipose stem cell populations. Moreover, the *in vivo* implantation experiments described in Example 5 of WO 00/53795 were carried out using athymic mice, i.e. mice whose immune system has been neutralized to avoid the risk of immune rejection. This strongly suggests that the cells have HLA Class I surface molecules. Consequently, WO 00/53795 does not describe cells having an HLA Class I negative phenotype.

Normal karyotype: No information is provided in WO 00/53795 with respect to the karyotype of the cells. In the absence of any cytogenetic analysis, no conclusion concerning the karyotype of the cells can be drawn. Again this characteristic is *not* inherent to all adipose-derived multipotent cells, particularly since the cells described in WO 00/53795 are said to be maintained in culture *in vitro* throughout at least 15 passages, which may induce neoplastic transformation, characterized by an abnormal karyotype.

Capacity to become quiescent: WO 00/53795 does not disclose the capacity of the cells to become quiescent. Again, this characteristic is not possessed by all multipotent cells, and is *not* an inherent characteristic as suggested by the Examiner. In the absence of information in this respect, it cannot be concluded that the cells described in WO 00/53795 have the capacity to become quiescent.

Self-renewal capacity preserved for at least 130 population doublings: It is stated at page 5 (lines 3 to 5) of WO 00/53795 that the cells can be passaged at least 15 times without losing their developmental phenotype. However, the number of population doublings to which 15 passages corresponds is not given, and cannot be calculated.

Moreover pending claim 1 requires that the self-renewal capacity be preserved for at least 130 population doublings. This means that the initial characteristics of the cells (i.e., those listed in claim 1) are conserved without change throughout all the population doublings. WO 00/53795 does not describe cells having such a characteristic.

In addition, the Examiner has stated that the cells according to WO 00/53795 are produced by processes which are identical or substantially identical to those disclosed in the present application. This is not correct. WO 00/53795 describes a process which is significantly different from that disclosed in the present application. In particular, the process according to

WO 00/53795 does not comprise a step of selection of two sub-populations, one having an adhesion rate of less than 12 hours and the other having an adhesion rate of more than 12 hours. Nor does it comprise a step of enrichment of the population with an adhesion rate of more than 12 hours (see for example pages 3 to 5 of WO 00/53795). The process employed in the present invention is thus different from that disclosed in WO 00/53795. As can be seen from "Katz II" (page 420, right hand column and page 421, left-hand column), differences in the process and handling conditions can lead to quantitative differences in the nature of the cells obtained.

Therefore, WO 00/53795 does not describe, either explicitly or implicitly, applicants' claimed cells.

Zuk et al.

The Examiner rejected claims 1-3, 49, 50, 53 and 54 under 35 U.S.C. §102(b) as being anticipated by Zuk et al. (*Tissue Engineering* 7: 211-228 (2001)).

The Examiner stated that Zuk et al. describes human processed lipoaspirate (PLA) cells which can differentiate into adipogenic, osteogenic, chondrogenic and myogenic lineages. The Examiner acknowledged that Zuk et a.l does not specifically teach that the cells have telomerase activity, an HLA class I negative phenotype, a normal karyotype, a capacity to become quiescent and a capacity for self-renewal preserved for at least 130 population doublings. However, the Examiner considered that these characteristics would be inherent to the cell isolated by

Zuk et al. because Zuk et al. allegedly teaches that the cells behave like human stem cells and 1 teaches method steps similar to those described in the subject specification.

Applicants respectfully submit that Zuk et al. does not anticipate the present claims. The cells described in Zuk et al. do not possess all the characteristics recited in the present claims. As discussed above and evidenced by "Katz II", adipose-derived multipotent cells do not all necessarily and inherently possess the claimed characteristics. Applicants note that the method used in Zuk et al. is identical to that used in "Katz II." Explicit reference to Zuk et al. can be found in "Katz II" at page 414, left hand column, line 10. Importantly, the cells obtained according to "Katz II", using the method of Zuk et al., are found to be *inter alia* : **MHC Class I positive** (see "Katz II", page 416, right hand column: "HLA-ABC" and Table 4), **telomerase negative** and **ABCG2 negative** (see "Katz II", page 422, left hand column and Abstract).

Again, it is clear that not all multipotent cell populations derived from adipose tissue have applicants' claimed characteristics, which include, for claim 1, an MHC Class I negative and telomerase positive phenotype, and for claim 53, an MHC Class I negative, telomerase positive and ABCG2 positive phenotype. Consequently, the claimed features are *not* necessary and inherent characteristics of adipose "stem" cells.

The following is also noted with reference to the disclosure of Zuk et al., compared to the features recited in pending claim 1:

Multipotent character: Although the LPA cell population of Zuk et al. was shown to be capable of giving rise to different cell lineages, the population is heterogeneous, and contains, *inter alia,* endothelial cells, smooth muscle cells and pericytes (see Zuk et al., page 217, lines 22 to 23, and lines 39 to 42 : page 223, lines 3 to 5). As confirmed at page 223 of Zuk et al., the apparent "multipotent" character *may* suggest the presence of a stem cell population but is not conclusive:

> *"Although the apparent multidifferentiative capacity of PLA cells suggests the presence of a stem cell population within human liposuctioned adipose tissue, it is not conclusive. Multilineage differentiation may also be due to the presence of (1) multiple lineage-committed progenitor cells ; (2) multipotent cells from other sources (e.g. pericytes, marrow-derived MSC's from peripheral blood); or (3) a combination of the above."* (Zuk et al, page 223, lignes 10 to 14).

The presence of multipotent cells therefore cannot be concluded from Zuk et al.

Applicants also note that Zuk, published a second paper in 2002 (Zuk et al. (2002) *Molecular Biology of the Cell* 13(12): 1059-1524) (hereinafter "Zuk II") which is attached hereto as **Exhibit B**. "Zuk II", which published after the priority date of the subject application, provides further information

concerning the LPA cell population. Specifically, "Zuk II" confirms the heterogeneous nature of the LPA cell population, and states that it is critical to establish clonal populations before being able to conclude that the cells are multipotent stem cells):

> *"PLA multi-lineage differentiation may result from the commitment of multiple lineage-specific precursors rather than the presence of a pluripotent stem cell population. Therefore the isolation of clones derived from single PLA cells is critical to their identification as stem cells."* ("Zuk II", page 4292, lignes 15 to 18).

This step of cloning is not described in *Zuk et al.* (2001), and therefore it cannot be concluded that any one isolated cell was multipotent.

Other characteristics recited in claim 1: With respect to the remaining characteristics recited in claim 1, Zuk et al. (2001), provides no information with regard to telomerase activity, or an HLA Classe I negative phenotype of the LPA cells. As discussed above, cells isolated using the method of Zuk et al. are seen to be HLA Classe I positive and to have no telomerase activity. Furthermore, there is no indication with regard to the karyotype of the cells or their capacity to become quiescent. Concerning the self-renewal capacity of the PLA cells, it is indicated at page 217 (lines 1 to 3) of Zuk et al. (2001) the PLA population can be maintained in culture *in vitro* for 13 passages (165 days in culture) without losing

its capacity to proliferate. As indicated in Figure 1B at page 216 of Zuk et al. (2001), in the conditions employed, 13 passages correspond to approximately 20 population doublings, and not 130 population doublings as required by the pending claims. Moreover, there is no indication as to the capacity of self-renewal (unchanged) of the LPA cells.

Applicants also note that Zuk et al. (2001) describes a process which is significantly different from that disclosed in the present application. In particular, the process according to Zuk et al. does not comprise a step of selection of two sub-populations, one having an adhesion rate of less than 12 hours and the other having an adhesion rate of more than 12 hours. Nor does it comprise a step of enrichment of the population with an adhesion rate of more than 12 hours. The process employed in the present invention is thus different from that described in Zuk et al. As discussed above, differences in the process and handling conditions can lead to quantitative differences in the nature of the cells obtained.

Accordingly, applicants maintain that Zuk et al. does not describe, either explicitly or inherently, the subject matter of applicants' pending claims.

In view of the above remarks, applicants maintain that claims 1-3, 49, 50, 53 and 54 satisfy the requirements of 35 U.S.C. §102(b) and respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Summary

In view of the amendments and remarks made herein, applicants maintain that the claims pending in this application are in condition for allowance. Accordingly, allowance is respectfully requested.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the enclosed $1,020.00 fee for a three-month extension of time, is deemed necessary in connection with the filing of this Amendment. If any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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